Gold-Coated NIR Stents in Porcine Coronary Arteries

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Background—As endovascular stents are altered to add functionality, eg, by adding radiopaque coatings, biocompatibility may suffer.

Methods and Results—We examined the vascular response in porcine coronary arteries to stainless steel gold-coated NIR stents (7-cell, Medinol, Inc). Stents, 9 and 16 mm in length, were left bare or coated with a 7-μm layer of gold. Physical and material effects were examined in four different gold-coated stent types, two at each length that either had the coating applied to the standard strut, ie, gold coated thicker than controls, or had the coating applied to thinned struts, ie, gold coated of the same thickness as control struts. Simple gold coating exacerbated intimal hyperplastic and inflammatory reactions over 28 days, but postplating thermal processing smoothed the coating surface and negated the adverse tissue response to gold. The relative amounts of base steel and gold coating and their resistances to expansion and collapse determined the extent of stent recoil.

Conclusions—Gold coatings enhance the radiopacity of steel stents, but not without effects on vascular repair. Material effects predominate and can be abrogated by heating coated stents to alter surface finish and material purity. Clinical results may suffer unless consideration is given to material and physical effects of gold. **(*Circulation*. 2001;103:429-434.)**

Key Words: restenosis ■ stents ■ thermal processing ■ vasculature ■ vascular repair

As novel designs and surface preparations have produced endovascular stents with dramatically reduced thrombosis and restenosis, the focus now is on increasing ease of use. Radiopacity in particular is poor with stainless steel and worse when struts are made thinner or spaced farther apart. Changes in design, material, or surface coatings that increase opacity cannot reduce overall functionality and biocompatibility. Stainless steel enables stents to be expanded within tortuous and eccentric lesions. Other metals and materials may not have dynamics that are as favorable. Similarly, as the biological sequelae of implantation are increasingly well defined, it becomes clear that stainless steel is relatively inert within the vasculature. Metal coatings may alter every phase of the response to vascular implantation, including thrombosis, inflammation, and proliferation.

Gold in particular has been touted as a potential coating for stents. Of all the radiopaque metals, gold is the easiest to work with by virtue of its low melting point and high malleability. On the other hand, there are disturbing reports that gold-coated stents incite an exaggerated vascular response.[1] We sought to define the biological reaction to gold-coated stents implantation and to determine whether the response stemmed from a fundamental limitation of the physical and material effects of gold or the processes by which the metal was applied.

Methods

Stents

Seven-cell stainless steel NIR stents (Medinol, Inc), 9 and 16 mm in length, were left intact or coated with a 7±2.5-μm gold layer. The 2-step plating process included generation of a "seed layer" to optimize adherence before plating. Because gold plating increased strut thickness by twice the coating depth, stents were electropolished to remove an equivalent 7 μm of steel from all sides of the struts before plating to maintain constant strut dimensions. In all, 5 different gold-plated stents were examined, and each coated stent was compared with uncoated devices subjected to identical processing except for gold plating. The performance of each set of gold-coated stents was compared with that of matched stainless steel controls taken from the same lot of material. Four sets of studies were performed. In the first two, 16-mm stents were used; in the latter two, 9-mm stents were used. In studies 1 and 4 (Table), when the coating was applied, the strut thickness was increased by the twice the thickness of the gold coating. In studies 2 and 3, stent struts were electropolished before coating so that the thickness after gold coating was identical to that of the standard stainless steel stents (the Table). As a frame of reference using a known standard, in concert with study 2, three animals received a single stainless steel Palmaz-Schatz stent (Cordis/Johnson and Johnson) in two coronary arteries. In a final set of experiments, the standard gold coating was compared with gold coating subjected to a thermal processing step intended to smooth the gold surface and potentially remove embedded impurities.

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Stainless Steel and Gold-Coated Coronary Arterial Stent Implant Studies

	n	Coating	Balloon:Artery	Intimal Thickness, mm	Injury Score	Recoil, %	Lumen, mm²
Study 1, 16-mm standard strut							
	9	None	1.08±0.03	0.19±0.03	0.05±0.02	22±5	3.29±0.38
	9	Gold	1.08±0.02	0.24±0.04	0.05±0.02	11±5*	4.19±0.50
Study 2, 16-mm polished strut							
	6	None	1.15±0.03	0.21±0.03	0.02±0.18	13±1	4.52±0.59
	6	Gold	1.13±0.01	0.26±0.05	0.06±0.08	17±1*	4.01±0.72
	6	Palmaz-Schatz	1.24+0.03	0.34+0.04*	0.62 +0.27	20 +1	2.21+0.39*
Study 3, 9-mm polished strut							
	6	None	1.09±0.04	0.28±0.03	0.08±0.03	10±3	5.10±0.54
	6	Gold	1.08±0.06	0.37±0.04	0.19±0.11	18±3*	3.07±0.45*
Study 4, 9-mm standard strut							
	8	None	1.13±0.06	0.14±0.02	0.02±0.01	15±1	4.59±0.70
	7	Gold	1.03±0.03	0.21±0.05*	0.16±0.01*	18±2	4.04±0.53
	7	Baked	1.12±0.02	0.15±0.02	0.01±0.01	17±2	4.61±0.42

*Statistically different ($P<0.05$) from controls.

Topographical and Elemental Analyses

The surface of the gold-coated stents was evaluated before and after heat treatment. Surface morphology was determined via an SEM (Leo 438VP) with a backscatter detector (Leo 400 Centaurus BSD). Elemental analysis was performed with energy dispersive x-ray spectroscopy (IXRF Analyzer, model 500). Auger electron spectroscopy (PHI 660) examined the outer stent surface. Surface topography was defined with atomic force microscopic analysis (Topometrix Explorer) of 10×10-μm areas and on two linear scans across the face.

Surgical Procedure

Seventy-eight stents were implanted[2] in 40 domestic swine (weight, 30 to 40 kg). Thirty-five animals survived perioperatively; those that died were excluded from further analysis. Animals were fed standard chow and water, and aspirin (325 mg, Sigma Chemical Co) was administered once daily throughout the postoperative period from the day before surgery. After anesthesia induction, animals received nifedipine 10 mg SL, bretylium 5 mg/kg IV, and cefazolin 500 mg IV. A 7F coronary guiding catheter (AR1 or Hockey Stick, Scimed Life Systems) was advanced to the coronary ostia via the right femoral artery. After administration of heparin (200 U/kg IV) and nitroglycerin (100 μg IC), angiography of the left and right coronary arteries was performed in orthogonal planes. Sections of each coronary artery judged to be 2.5 to 3.5 mm in diameter were chosen for stent deployment. A single standard stainless steel or gold-coated stent was placed in two of the three arteries.[2] All stents were mounted on 3.0- to 4.0-mm angioplasty balloons (20 mm, SCIMED Ranger) to provide ratios of balloon/stent to artery of ≈1.1:1. Stents were advanced over an angioplasty guidewire (High Torque Floppy, Guidant, Inc) to suitable segments of the coronary artery and inflated at 8-atm pressure for 30 seconds. Nitroglycerine 100 μg IC was again administered, and angiography was repeated in orthogonal views. On completion of the procedure, the femoral artery was ligated, and cefazolin 500 mg IV was administered. The ratios of balloon/stent to artery were calculated angiographically from balloon and preplacement lumen diameters measured with digital calipers offline on cine film.

Twenty-eight days after implantation, animals were anesthetized and euthanized with KCl 40 mEq IV. The hearts were removed, and the coronary arteries were perfused with Ringer's lactate solution infused into the aortic root at 100 mm Hg, followed by 4% paraformaldehyde in 0.1 mol/L sodium phosphate buffer fixative. The coronaries were dissected, and stented sections were isolated and immersion fixed in 4% paraformaldehyde fixative. Stented arterial segments were oriented longitudinally and embedded with a methacrylate formulation.[3] Multiple sections 5 μm thick were cut with a tungsten carbide knife (Delaware Diamond Knives) on an automated microtome (Leica, Inc) from the proximal and distal ends and the midpoint of each stented segment. Sections were stained with hematoxylin and eosin and with ver Hoeff's elastin stain. Computer-assisted digital planimetry measured lumen, neointimal, and medial cross-sectional areas. Luminal diameter was calculated from luminal area, and stent diameter was calculated from the area bounded by the internal elastic lamina. Histological late loss of luminal diameter was calculated as the difference between stent and luminal diameters. Recoil was calculated as the difference between balloon size at implantation and histologically determined stent diameter. Inflammation was determined by quantitative determination of the number of multinucleated giant cells and by immunostaining for porcine CD45 (allotypic variant, Serotec Ltd) with a low-temperature antigen retrieval and a tyramide signal amplification system kit (Dako, Inc). The percent of immunopositive CD45 cells was semiquantitatively measured in the neointima in 5 fields.[4] Injury scores were determined as described.[5]

Statistical Analysis

For each stented segment, results from each end and the middle were averaged to minimize sampling error. Data are presented as mean±SE. For each of the four studies, coated and uncoated groups were compared with the use of unpaired Student's t test, with $P<0.05$ considered significant. ANOVA was used for comparisons of the three groups in the fourth study.

Results

Topographic and Elemental Analysis

The surface of the gold-plated stents is evident in the microscopic images (Figure 1). The roughness of the standard gold plating was equivalent to that of standard stainless steel, and heat treatment smoothed the surface of the gold plating without erosion. Heated gold layers were smooth but thin enough to reveal the underlying granular interface of the stainless steel (Figure 1c and 1d). The differences between

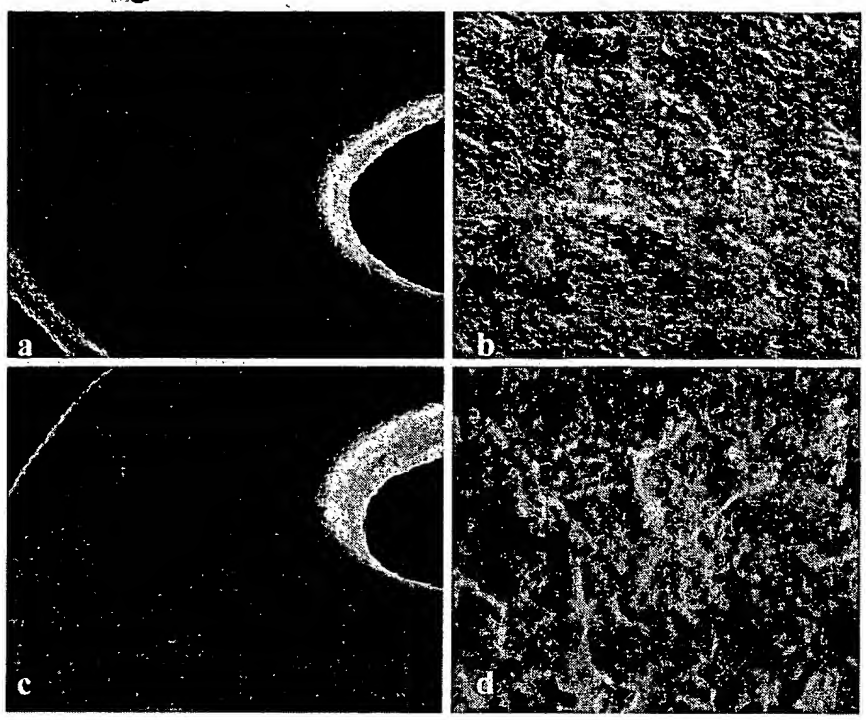

Figure 1. SEMs of gold-plated NIR stent surfaces (a, b) and after heat treatment (c, d) at ×350 (a, c) and ×1500 (b, d).

the surfaces were confirmed by atomic force microscopy. The average roughness of the unheated gold-coated stents was more than twice the value for heated stents, with a 3.3-fold–greater mean peak-to-valley height in profile (Figure 2). Although surface roughness was reduced with heating, there was no discernible difference in surface elemental density by energy dispersive x-ray spectroscopy or Auger analysis between the nonheated and heated surfaces. More iron was detected to have diffused into the gold coating of the heated stent, but in none of the stents did iron reach the stent surface. Initial Auger surveys of the gold-coated and heated gold-coated stents showed only oxygen and carbon at the outermost surface. After several cycles of sputtering, the carbon layer was greatly reduced, and only gold was detected. No trace contaminants were detected on the surface of the stents.

Biological Response

The biological responses to stainless steel and gold-coated stents 28 days after implantation were compared. Ratios of balloon to artery for all devices ranged from 1.03 to 1.2 (the Table) and did not correlate with ultimate neointimal size. Two different stent lengths (9 and 16 mm) were examined, and the coating either was applied to struts whose thickness was equivalent to that of the control stents or reduced by twice the thickness coating depth. No stents were thrombosed at harvest. Differences were observed in the reaction of stainless steel stents of different dimensions (Table); comparisons were made only within specific experiments, not across experiments.

In every experiment, gold-coated stents produced a greater neointima than their stainless steel counterparts, the difference being more profound with shorter stents. Neointimal thickness was increased by 24% and 26% in the long stents and by 33% and 57% in the short stents of standard and thinned strut thicknesses, respectively (the Table and Figure 3). In marked contrast, heat processing rendered the responses to gold-coated stents indistinguishable from uncoated stainless steel stents (Figure 3). Although the injury scores in all sections were low (<0.2), in all but study 1, they were higher in the gold-coated stents. Because the ratios of balloon to artery were similar between stent types, the observed differences in injury score likely reflect late effects rather than acute implantation-related injury alone. Palmaz-Schatz stents provoked greater intimal thickness (0.34±0.04 mm) at

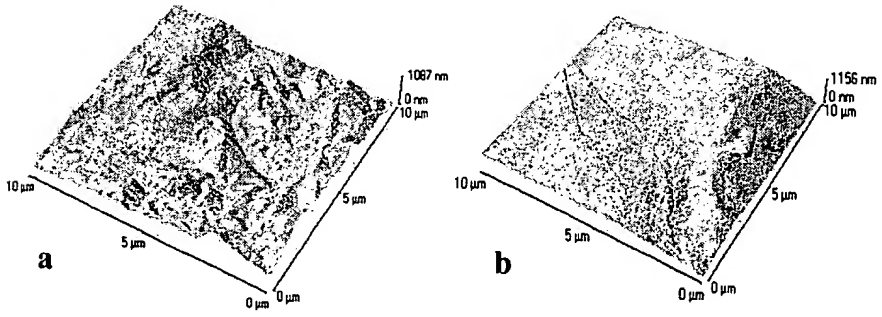

Figure 2. Three-dimensional atomic force micrographs demonstrated surface topography of gold-coated NIR stents before (a) and after (b) heat treatment. Average roughness of heat-treated stents was less than half of nonheated gold stents (59.9±22.4 vs 154.6±5.4), and mean maximum peak-to-valley excursion was >3-fold lower (86.4±7.7 vs 284.4±3.9).

a higher injury score (0.6±0.3) with lower lumen areas (2.21±0.4 mm^2) than any of the gold-coated devices.

The reduction in neointima with thermal processing of gold-coated stents correlated with a reduction in inflammation to levels equivalent to uncoated stents. The number of porcine CD45-positive cells per five high-power neointimal fields in nonheated gold-coated stents (134.0±18.5) was 2.6-fold greater than the reaction in uncoated stainless steel stents (45.6±9.1) or heated gold devices (41.3±7.6, $P<0.0001$; Figure 3). Similarly, CD45-positive cells in the neointima represented 14.8±0.4%, 5.6±0.8%, and 5.7±1.5% of the total cells for steel, gold-coated, and heated gold stents, respectively, and the number of multinucleated giant cells increased in gold-plated but not heated gold-coated stents: 8.4±0.6, 13.2±2.2 ($P<0.02$), and 8.6±0.9 giant cells per section for steel, gold-coated, and heated, gold-coated stents, respectively.

Strut Thickness

The application of a coating by necessity changes the thickness of the stent strut. We examined struts of two thicknesses, one that increased the strut thickness by virtue of the gold coating and one with the same strut thickness achieved by electropolishing of the steel stent before coating. When the coated stent struts were polished to equalize coated and uncoated stent thickness, there was less stainless steel and more soft gold in coated struts, and these stents exhibited a greater propensity for recoil (Table). Correspondingly, when the amount of steel was kept constant and the gold-coated struts were therefore thicker, recoil dropped. The impact of recoil on luminal diameter is synergistic with intimal hyperplasia. For example, recoil was so much less in the coated 16-mm stents when the 7-μm coating was added to a standard thickness strut that the ultimate lumen size was greater for the gold-coated stents despite greater tissue growth.

Discussion

As endovascular stents are altered to add functionality, biocompatibility may suffer. Indeed, gold coatings of a stent type other than that used here elicited greater restenosis than similar uncoated stainless steel devices.[1] We now report that although gold coating of stainless steel improves radiopacity, the mode of coating processing determines the hyperplastic and inflammatory reactions. The reduced compatibility of gold-coated stents was completely negated by postplating heating. Moreover, the relative amounts of base and coating metals, and their respective resistances to expansion and collapse, determine stent recoil.

Biomedical Applications of Gold

Because of its malleability and relatively low melting point, gold is one of the easiest metals to manipulate, and for >5000 years, gold has adorned jewelry, weapons, goblets and silverware, homes, and statuary.[6] Gold dental fillings and prostheses were used >3000 years ago.[7–9] Early rehabilitation in facial nerve paralysis involved placement of gold weights or springs in the lower eyelid,[10] and gold materials were a major part of cranioplasty.[11] Gold has been used in electromechanical devices by virtue of high electrical conductivity and corrosion resistance and in a broad spectrum of applications in biology, pharmacology, and medicine. The

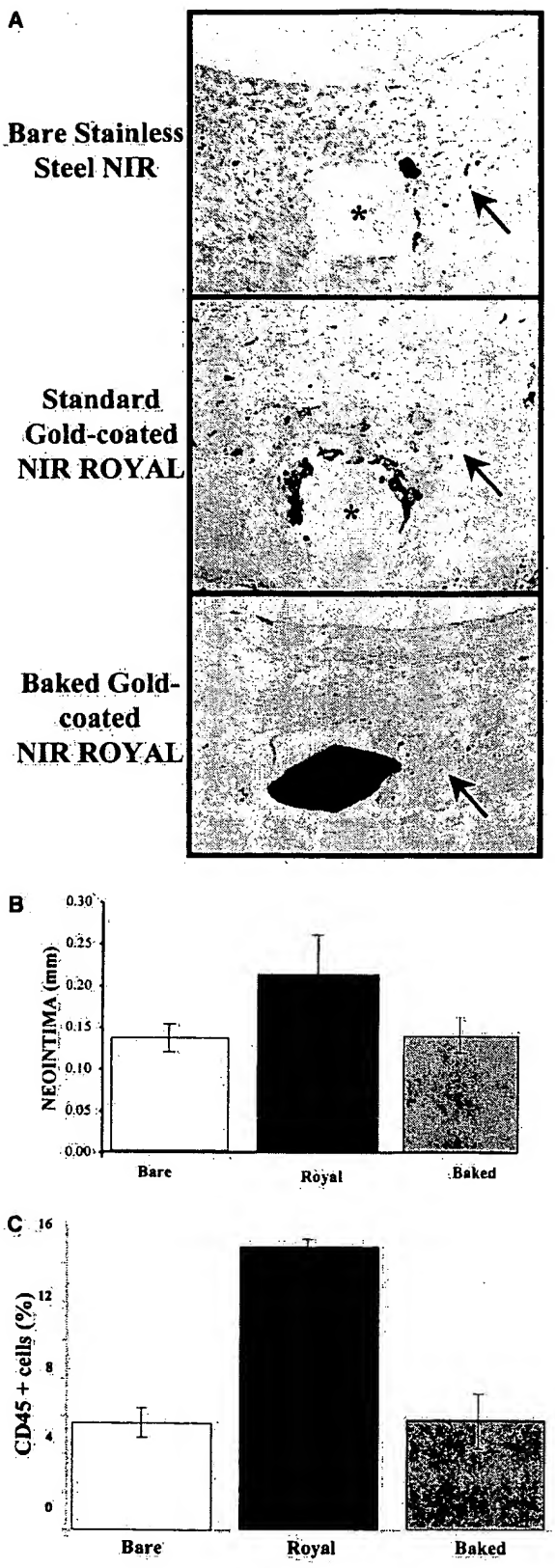

Figure 3. Photomicrographs (a; ×200), extent of neointimal thickness (b; mm), and degree of inflammation (c; % porcine CD45-positive cells in neointima) 28 days after implantation of 9-mm stainless steel stents left intact (Bare; open bars), gold-coated NIR stents (Royal; solid bars), and flash-heated post-plated NIR stents (Baked; gray bars). Arrow indicates internal elastic lamina; *, sites of stent struts.

cellular compatibility of this material is high, as evidenced by its use as a tracer compound following cell motility and defining cell structure with electron microscopy. Ease of use, coupled with atomic weight and density, might make gold a natural material for enhancing endovascular implant radiovisibility. Gold is, however, subject to corrosion in chlorine-rich environments and is perhaps 100 times less resistant than 316L stainless steel.[12] Thus, a central question is whether stents with surface gold would elicit untoward tissue responses and, if so, whether such a response was an obligate material reaction or controllable through manipulation of metal or surface properties.

Our knowledge of gold biocompatibility stems in part from studies of the effects of dental prostheses and other gold-plated implants. The most biocompatible of six single-phase dental metal alloys was the one with the greatest gold content.[13] Gold has been used to mark catheters, the ends of balloons, portions of guidewires, and stents. Gold markings have extended from isolated dots to coatings over terminal rings or the entire stent surface. The juxtaposition of two dissimilar materials and differences in surface and mechanical properties can generate profound effects. Surface applications that remove the oxide layer that covers stainless steel may make this inert material less compatible. Surface modifications can create substrate-film mismatches, film defects, volume changes, alterations in film microstructure, impurities, anisotropic growth, or electrostatic effects. Thus, the possibility of surface breaks and cracks from tensile stress or of buckling or curling with compression arises. Metallic coating alterations in charge, hydrophobicity, and texture, as well as surface composition, can influence thrombogenic potential, endothelial regeneration, and intimal hyperplasia. Rougher surfaces increase thrombosis, mural injury, intimal hyperplasia,[14] and altered endothelial cell migration,[15] and platelets adhere with greater affinity to materials with high surface potential materials and hydrophobicity.[16]

The earliest clinical use of gold-plated stents was in the genitourinary tract.[17,18] Gold-plated stainless-steel prostatic stents produced fewer acute irritative symptoms, no greater infections, and minimally greater encrustations than nitinol stents.[17] Gold-coated endovascular stents have also fared well, especially compared with other metals such as copper. Copper, but not gold,[19] increased the thrombogenic potential of stents, and gold-plated stents produced fewer macroscopic and histopathologic changes in dog aortae than silver- or copper-plated or Teflon- or silicone-coated devices. Copper-plated stents in particular eroded the vessel wall, with marked thrombus formation and aortic rupture.[20] Hehrlein et al[14] coated the surface of stainless steel Palmaz-Schatz stents with platinum, gold, or copper by electrochemical deposition or argon ion bombardment. Four weeks after implantation, 6 of 14 galvanized stents, but none of the uncoated or ion-bombarded stents, were occluded by a thrombus. Similarly, neointimal hyperplasia was increased in galvanized coated stents compared with stents coated by ion implantation. In both study groups, the most electropositive coating (platinum or gold) induced markedly less neointimal formation than the least electropositive (copper). Thrombogenic properties of bare and gold-coated stents in flow loops did not differ.[21]

Nonetheless, recent articles[1] have indicated that gold coatings on stents may not be as compatible as their stainless steel counterparts. Seven hundred thirty patients at a single center were randomized to receive a standard stainless steel or 5-μm gold-coated slotted tube stents. Stent occlusion at 30 days was 4-fold higher and the probability of death, myocardial infarction or target lesion revascularization after 1 year was almost twice as great in the gold-plated group. The stents used in that study (InFlow Gold) were different in design and material than those we examined, and the reaction to the gold coating reported in that study[1] was far greater than anything we observed. Gold-coated stents in our study failed to elicit a reaction greater than that observed in clinically used devices; the neointima formed in all of the gold-coated stents was less than that observed with Palmaz-Schatz stents placed in identical animals under similar conditions. Thus, it is increasingly clear that even subtle changes in the processing of metal plating can have profound effects on the biocompatibility of a coated device. Some gold-plating techniques clearly endow stents with an excessive inflammatory or proliferative reaction. However, others may not, and those that do can be made more compatible with additional processing.

Benefits of Postplating Processing

A number of possible interrelated effects might explain why heating gold-coated stents removed adverse material-tissue interactions, including smoothing of the stent surface, removal of impurities, and strengthening of the gold stent interface. The relative bioinertness of stainless steel arises primarily from the overlying oxide layer. Application of a metal coat requires removal of this layer. The intergranular spaces of the stainless steel must then be covered by the coating or establish nidi for corrosion and potential reservoirs for contaminants. Coatings that are incomplete, are highly porous, flake with wear, or crack with stent expansion expose the underlying metal. Organic contaminants, such as long-chain acids used as surfactants or cyanate salts used in plating process, can become trapped in these intergranular spaces. Heating can disintegrate these contaminants and smooth the surface of the gold coating. Average roughness values for the heated stents were half of the nonheated and comparable to plain stainless steel devices. Intergranular spaces or pores in a porous material within the coating might be sealed or covered over.

Noble metals are minimally chemically reactive, and within the transition elements, gold is the noblest. Mineral gold is not a pure metal but rather an alloy. Harvested ores may contain more silver than gold. Even gold processed to 99.99% purity retains 100 ppm silver, 20 ppm copper, and 30 ppm other base metals.[22] Although it is not clear whether these levels of impurities can alter tissue responses, minor amounts of nickel, molybdenum, and chromium eluted from metal stents can increase thrombogenicity and leukocyte activation in bench-top assays.[23] The diffusivity of a compound is temperature dependent, and at some temperatures, the diffusivity is so low that no movement can be detected. The distance one metal will traverse into another during heating is the square root of the product of the diffusivity of the one metal into the other at the specific heating temperature and the time that the material is exposed to that temperature. The diffusivity of gold into stainless steel is so low that it will not